DCC-3116, a First-in-Class Selective Inhibitor Of ULK1/2 Kinases and Autophagy, Combines with the KRAS^{G12C} Inhibitor Sotorasib Resulting in Tumor Regression in NSCLC Xenograft Models

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A Cancer Center Designated by the National Cancer Institute

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Martin McMahon, Disclosures:

Research Support:

- Deciphera Pharmaceuticals
- Revolution Medicines
- Pfizer Inc.

Honoraria:

- Deciphera Pharmaceuticals
- Revolution Medicines
- Pfizer Inc.
- Autobahn Labs
- Aro Biotherapeutics

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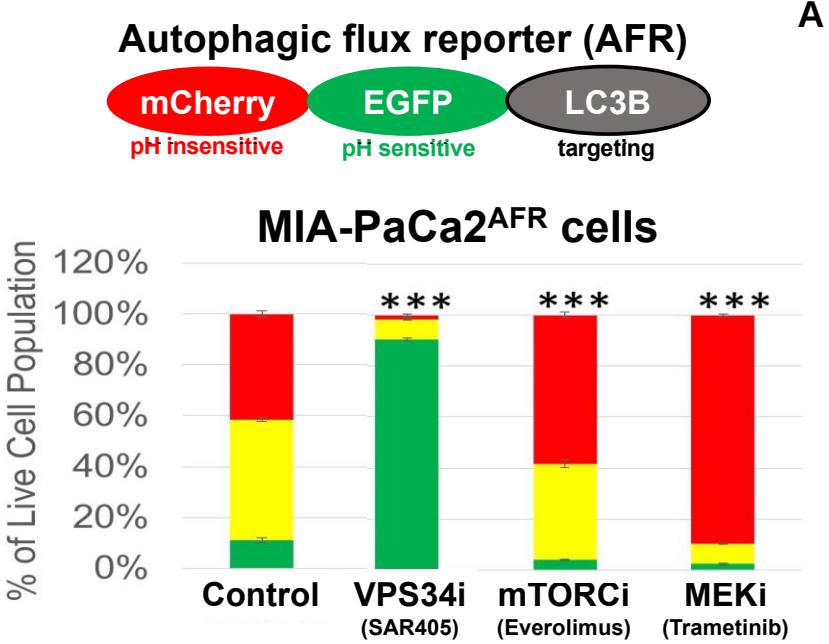
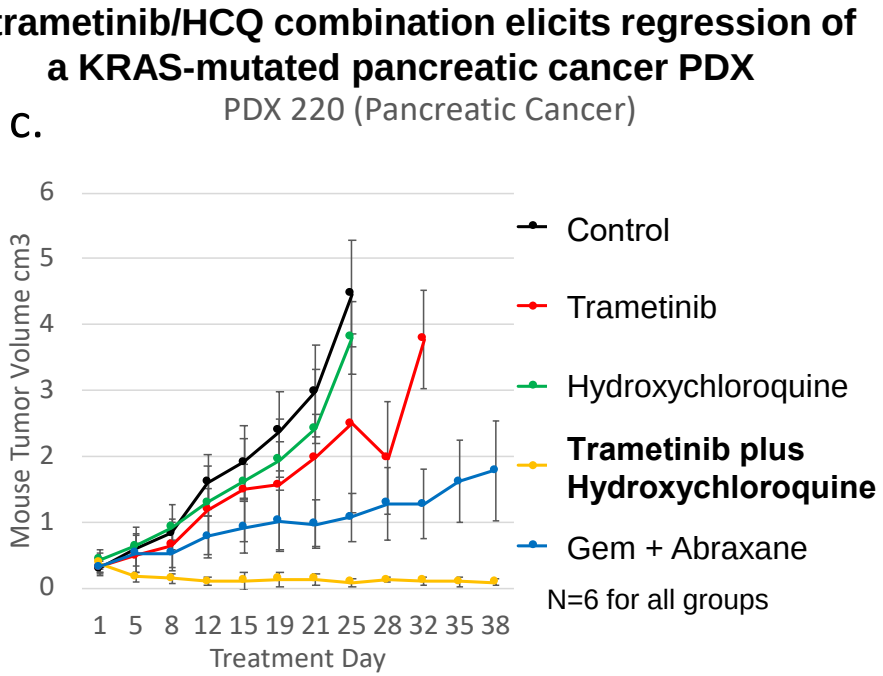
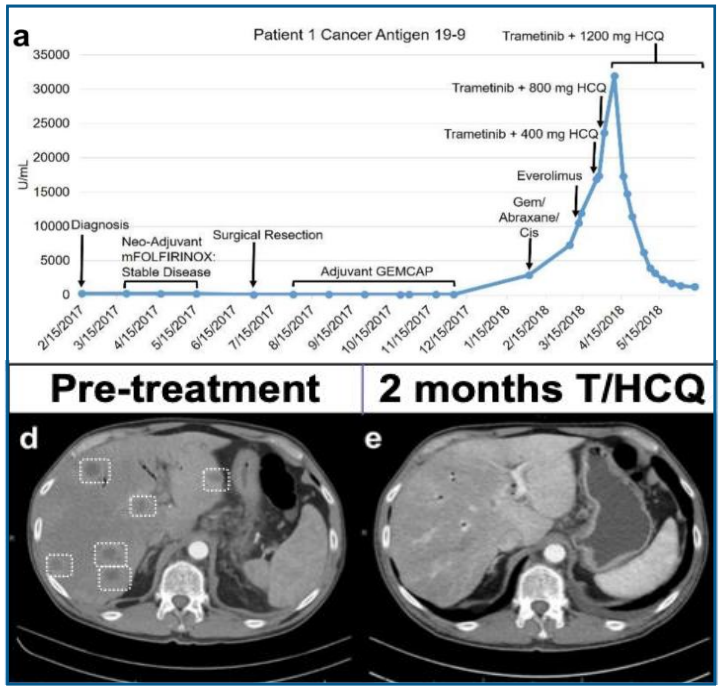
RAS oncoproteins as drivers of malignant transformation and as targets for pathway-targeted cancer therapy.

- Mutationally activated H-, K- or NRAS genes encode oncoproteins that drive the aberrant and lethal behavior of ~20% of all human cancers
- Once considered “undruggable”, RAS oncoproteins are now at the center of a massive effort to develop direct pharmacological inhibitors of RAS.GDP or RAS.GTP, representing a major advance for cancer therapy.
- However, as with most/all single-agent, pathway-targeted cancer therapies, the durability of patient response is limited by the emergence of drug resistant disease generally due to on-target reactivation of the RAS-regulated RAF>MEK>ERK MAP kinase and/or the PI3’-kinase>AKT signaling pathways.
- Hence, the depth and durability of patient responses will likely be greatly improved by the development of novel combination therapies whether it be RAS inhibitors plus: 1. Conventional chemoRx; 2. Radiation therapy; 3. immuno-oncology or; 4. Pathway-targeted agents.

Inhibition of KRAS>RAF>MEK>ERK signaling with trametinib in RAS-driven cancers induces cytoprotective autophagy







- **Inhibition of KRAS>RAF>MEK>ERK signaling in RAS-driven cancer cell lines leads to induced autophagy**

- **Combined inhibition of KRAS>RAF>MEK>ERK signaling plus lysosome function (HCQ) promotes regression of established xenografts**

- **Patient 1 showed a striking anti-tumor response to the combination of trametinib plus HCQ (T_2HCQ_{1200})**

Kinsey et al., (2019) *Nature Medicine*
McMahon Lab

Bryant et al., (2019) *Nature Medicine*
Der Lab

Lee et al., (2019) *PNAS*
Luo Lab

MEK1/2 inhibition leads to activation of the LKB1►AMPK►ULK1 signaling axis

Molecular Cell
Article

Molecular Cell (2009) 33(2):237-47

Oncogenic B-RAF Negatively Regulates the Tumor Suppressor LKB1 to Promote Melanoma Cell Proliferation

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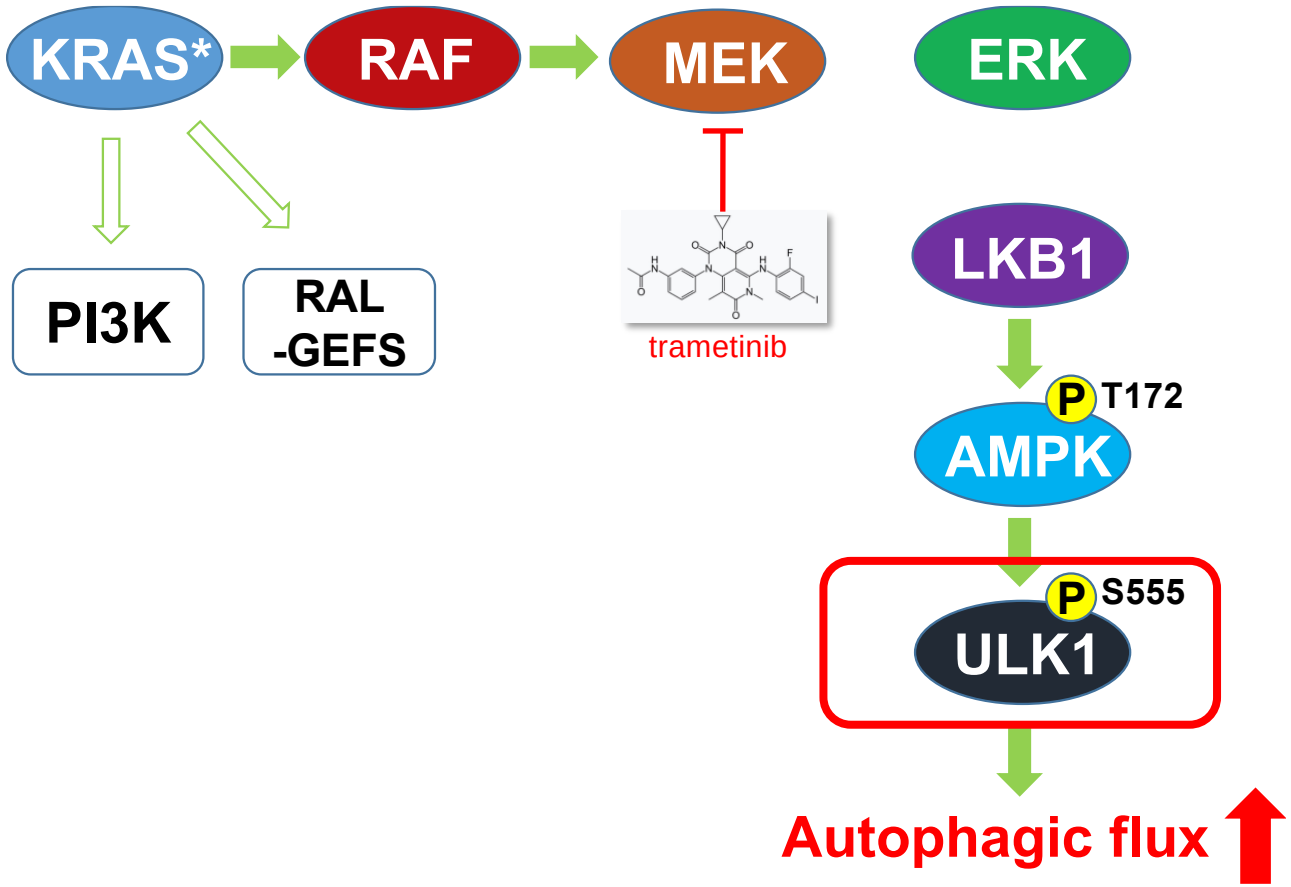
DOI 10.1016/j.molcel.2008.12.026



ULK1/2 Inhibitor (DCC-3116) Inhibits Autophagy Pathways Activated by Tumor-Targeted Therapies

>70% of human cancers depend on RTK/RAS/MAPK signaling.

- Inhibitors of tumor driver pathways activate ULK-dependent tumor survival pathways that mediate resistance through autophagy.

ULK1 and ULK2 kinases are initiating factors for activation of autophagy

- ULK inhibition leads to striking pre-clinical anti-cancer activity in combination with tumor driver inhibitors within the RTK/RAS/MAPK pathway.

DCC-3116 is the only selective and potent ULK kinase inhibitor in clinical development

- DCC-3116 is a First-in-Class target opportunity in RTK, RAS, MAPK mutant cancers. DCC-3116 is currently under clinical investigation (NCT04892017).

Phase 1 dose escalation includes rational combination cohorts

- Deciphera is on track to initiate combination cohorts by the end of 2022.

DCC-3116 is a Potent & Selective, First-In-Class ULK1/2 Inhibitor Designed to Inhibit Autophagy

Summary

Highly Potent (IC_{50} cellular NanoBRET)

- ULK1: **6nM**
- ULK2: **9nM**

High Kinome Selectivity

- No off-target kinases within 30-fold of ULK1
- Only 5 kinases within 100-fold of ULK1

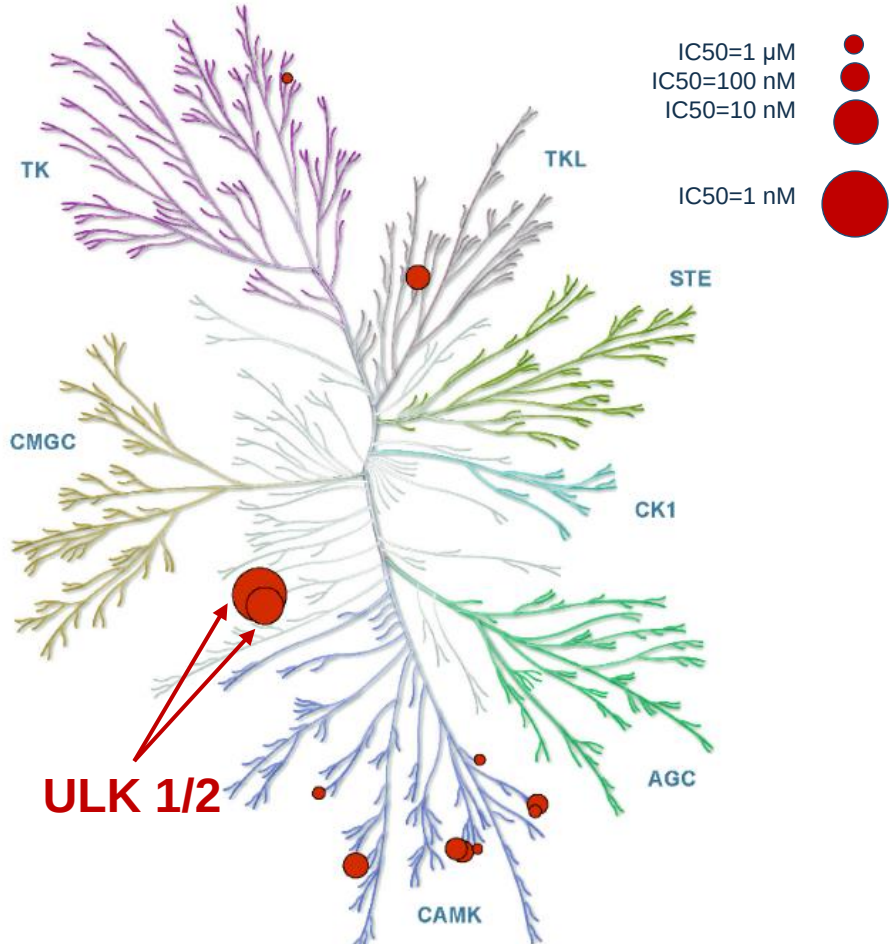
Designed to avoid CNS exposure

- Low Ratio $Brain_{ff}/Plasma_{ff}$ (4.3%) to avoid CNS autophagy

Phase 1 study initiated in June 2021

- NCT04892017

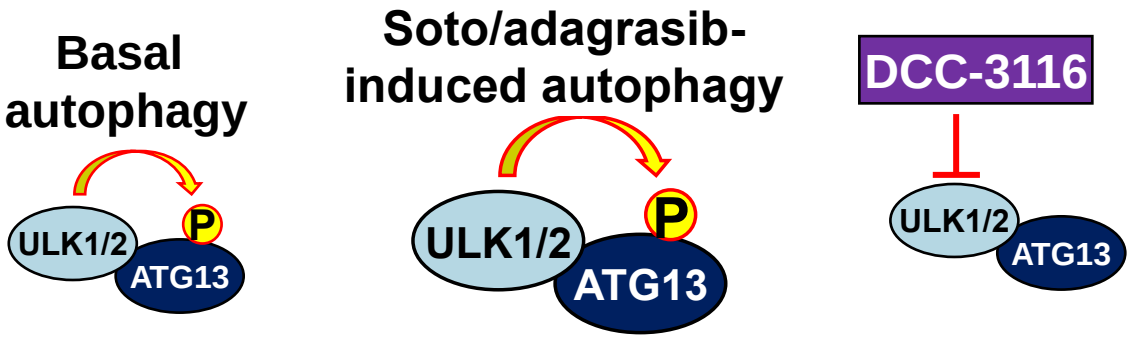
DCC-3116: A Selective ULK1/2 Inhibitor



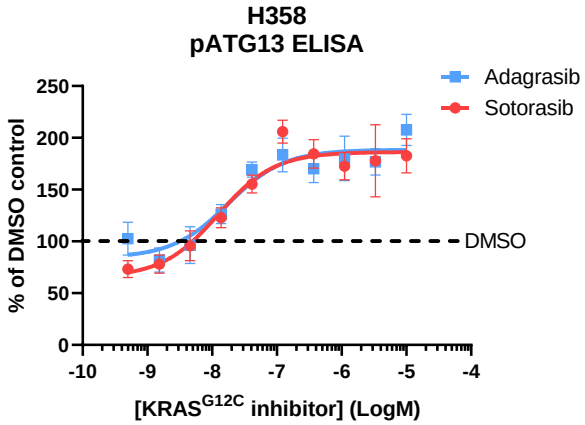
Source and Notes: Composite of enzyme and cellular kinase phosphorylation data was used. The size of the red circle corresponds to the IC_{50} value obtained. No circles are plotted for kinases with IC_{50} > 1 μM; Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

DCC-3116 inhibits ULK1/2 activity and autophagic flux in a KRAS^{G12C} mutated NSCLC cell line

DCC-3116 inhibits KRAS^{G12C} inhibitor-induced ULK → pATG13 signaling



KRAS^{G12C} inhibitors induce ULK activity



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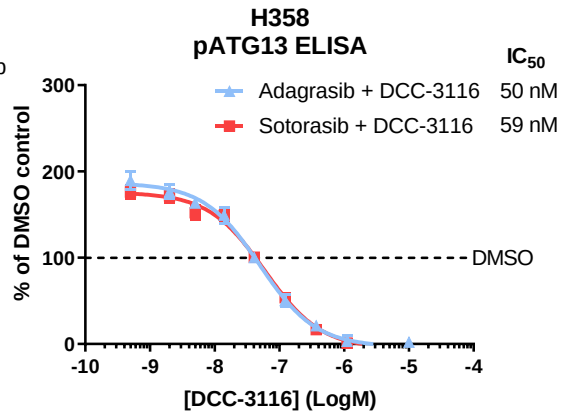

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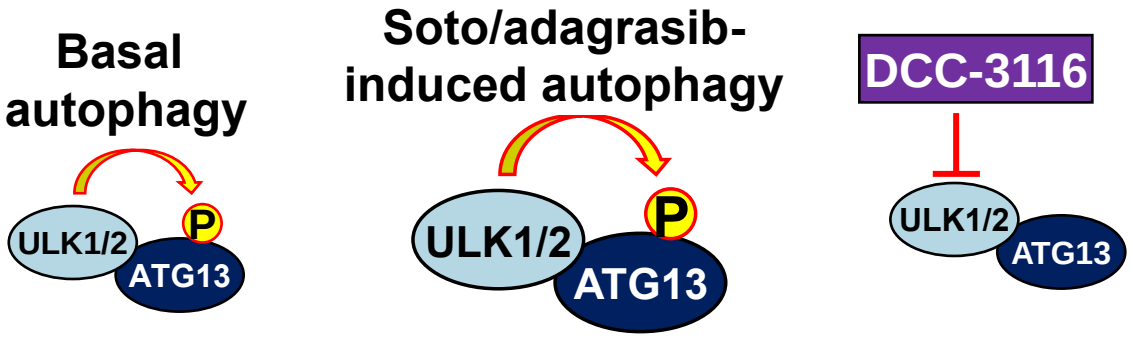

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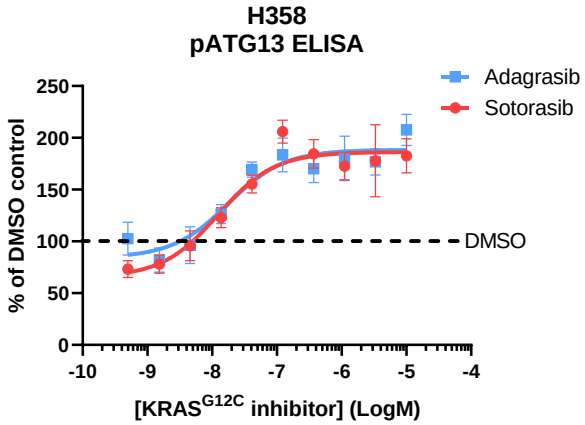

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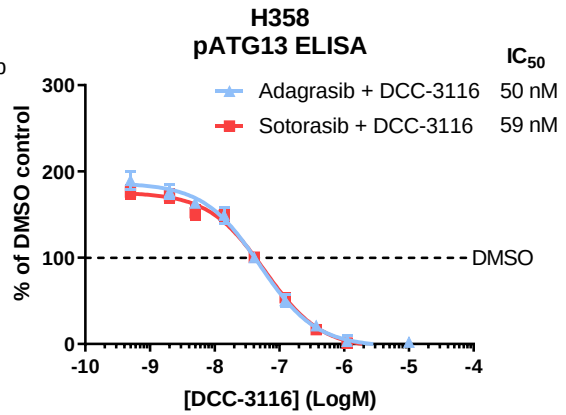
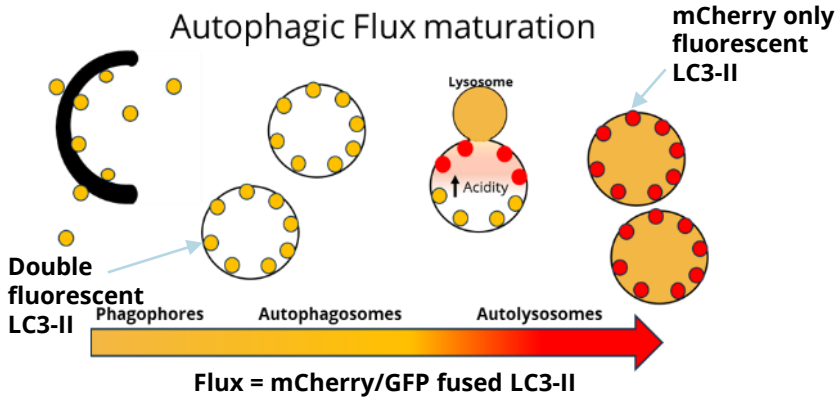
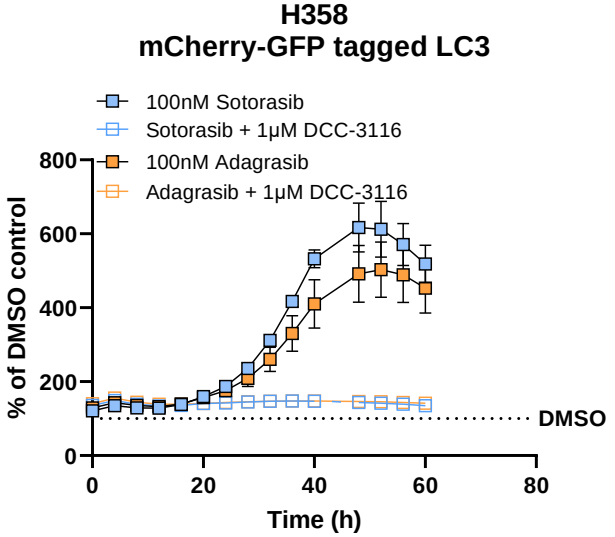
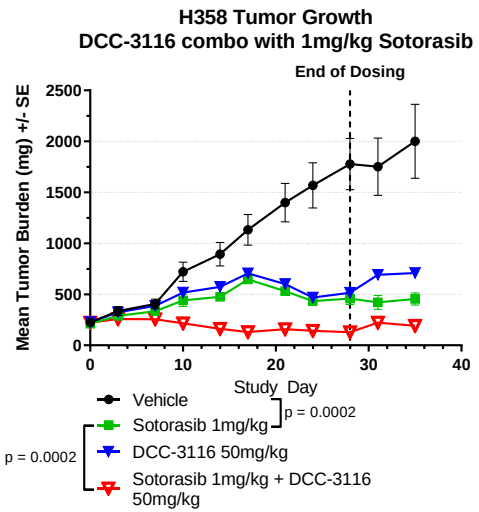


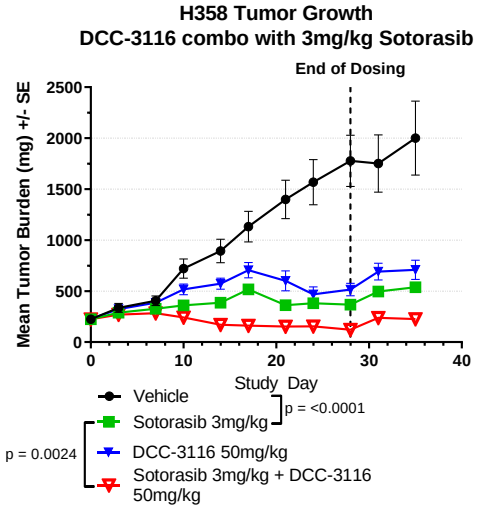
DCC-3116 inhibits KRAS^{G12C} inhibitor-induced autophagy flux

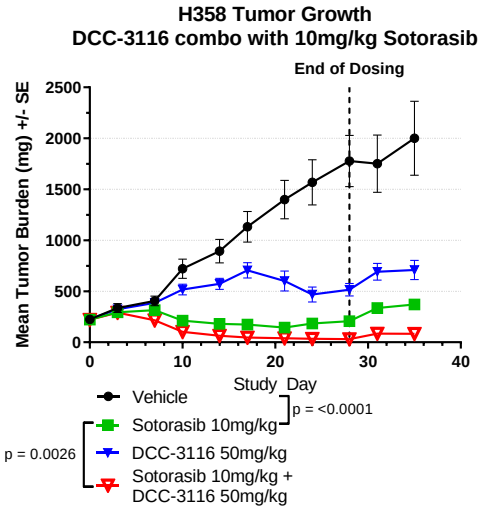


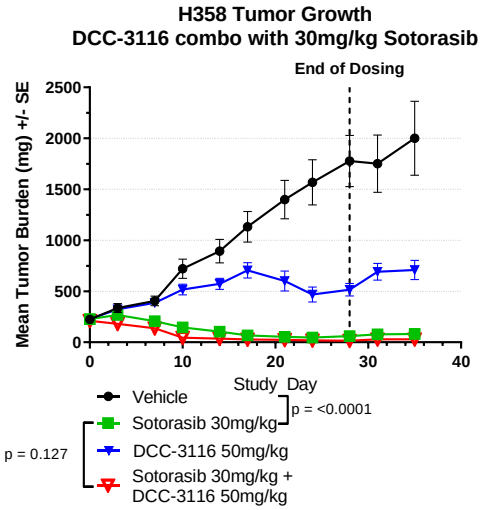


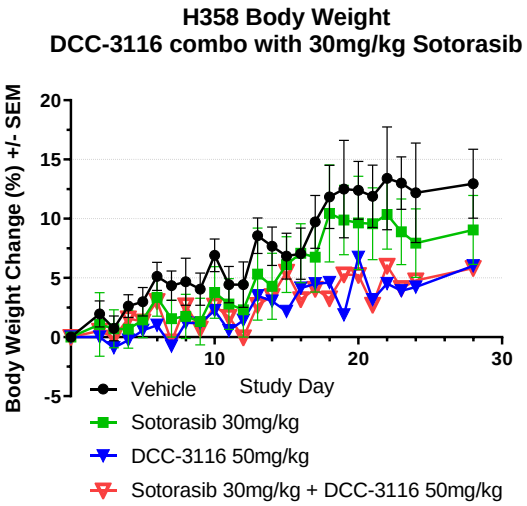
DCC-3116 produces deeper and longer regressions in combination with sotorasib in a KRAS^{G12C}-mutated NSCLC xenograft model



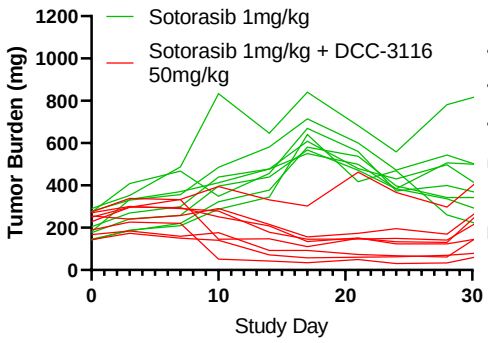


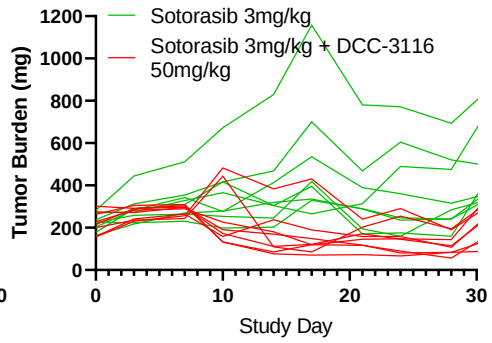


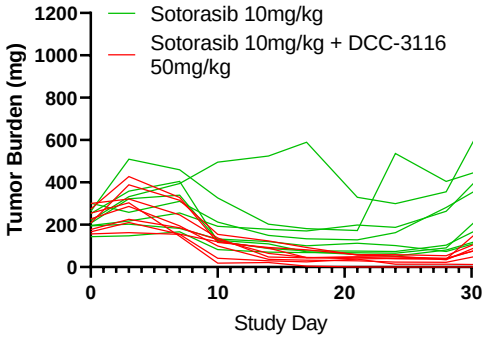


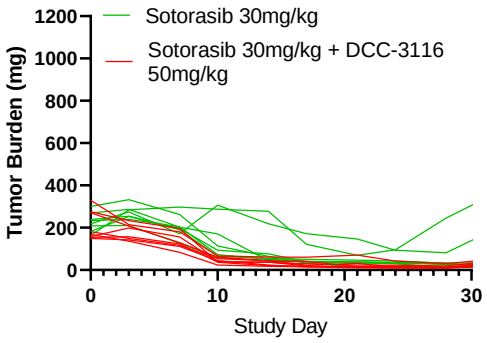


Spaghetti plots demonstrating sustained regressions in combination cohorts





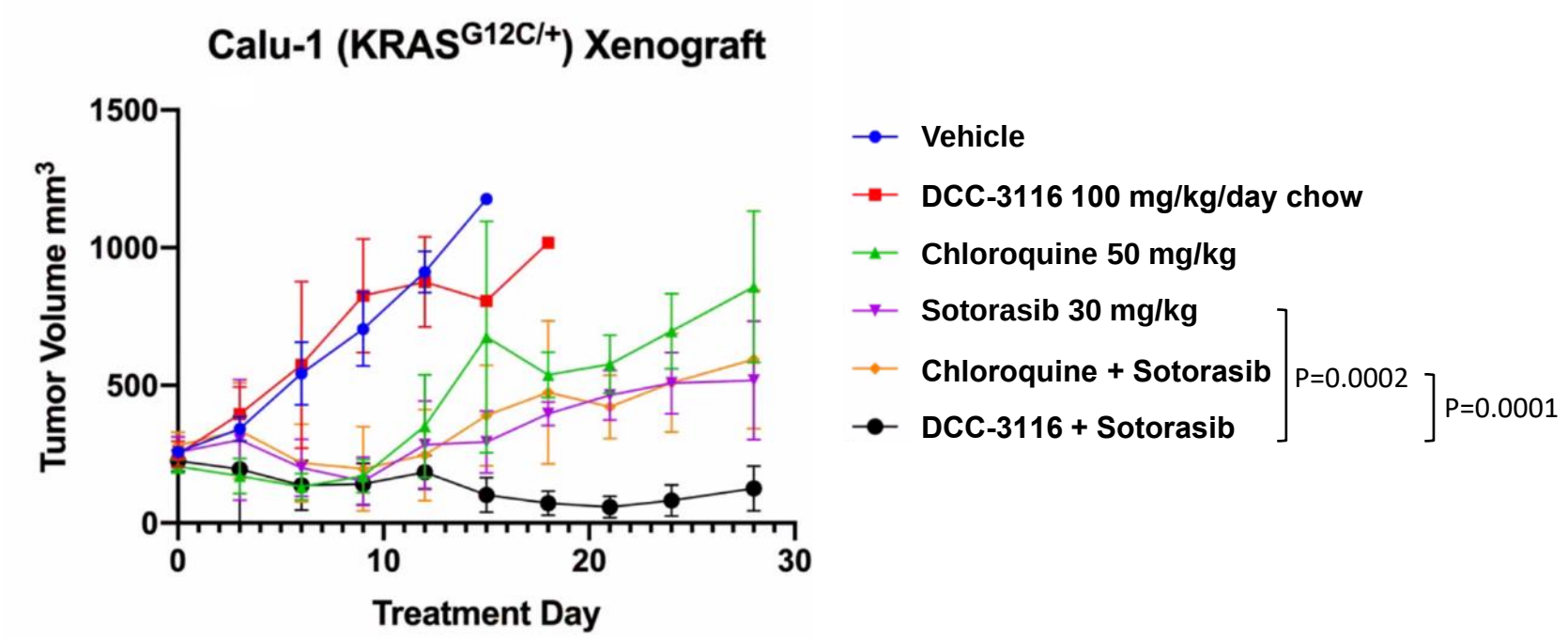




Sotorasib dosed QD and DCC-3116 dosed BID

DCC-3116 Outperformed Lysosomal Inhibitor Chloroquine as a Combination Partner to Sotorasib in a KRAS^{G12C} NSCLC Model

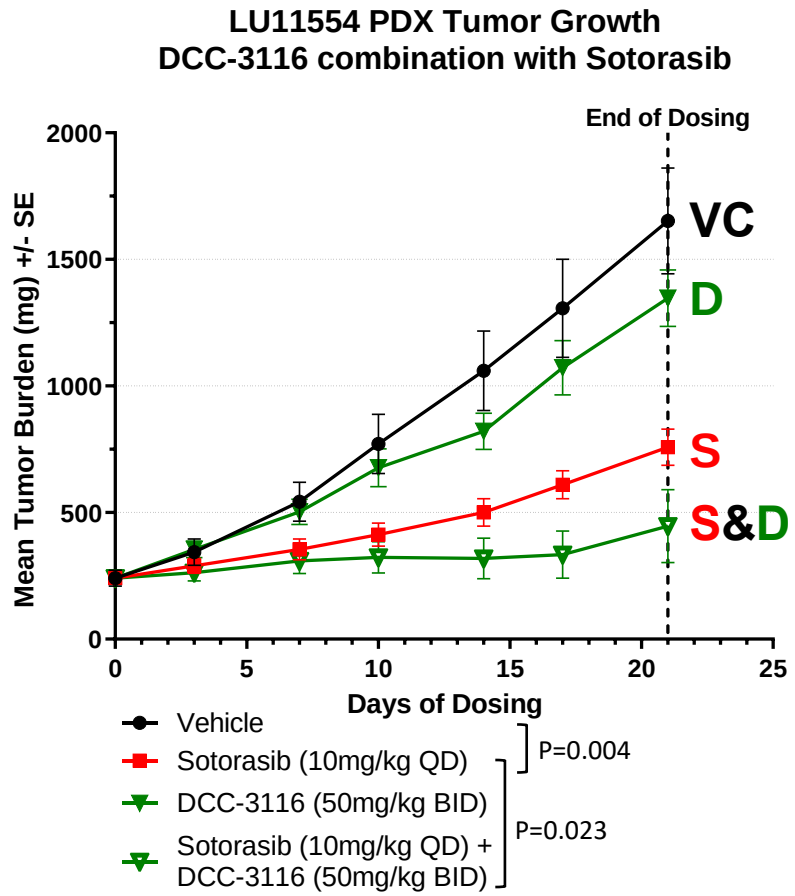
Calu-1 is a NSCLC xenograft model with a heterozygous KRAS^{G12C} mutation

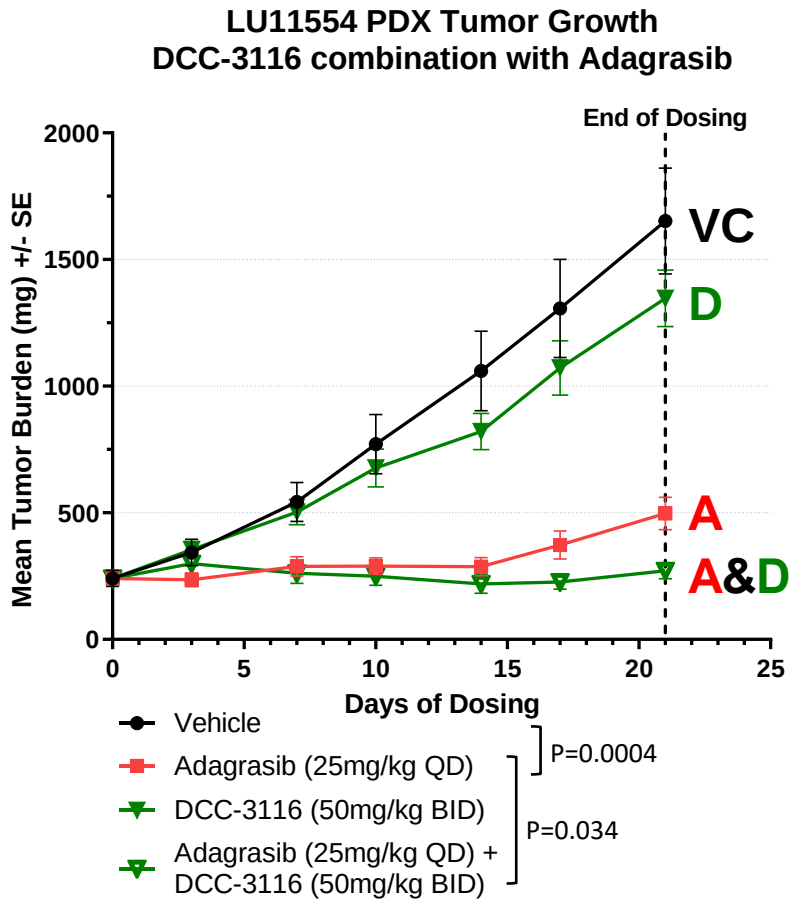


- DCC-3116 cooperates with sotorasib for superior control of Calu-1 KRAS^{G12C}-driven xenografts
- Combination sotorasib plus DCC-3116 elicits tumor regression

DCC-3116 Exhibits Combination Efficacy with Sotorasib and Adagrasib in a PDX Lung Cancer KRAS^{G12C} Model

LU11554 is a KRAS^{G12C}-driven NSCLC PDX model with *KEAP1* and *CDKN2A* mutations





Statistics: unpaired t-test, Day 17

Summary & Conclusions

- Inhibitors targeting mutant RTK>RAS>BRAF cancers activate ULK1/2-mediated autophagy as an adaptive treatment resistance mechanism
- Sotorasib and adagrasib activate ULK1/2-mediated autophagy that is inhibited by DCC-3116 *in vitro*. Combination therapy with DCC-3116 translates to deeper and longer tumor regressions *in vivo*
- These data demonstrate a compelling rationale to evaluate DCC-3116 in combination with $KRAS^{G12C}$ inhibitors in NSCLC patients
- DCC-3116 is currently in a Phase 1 clinical trial in patients with advanced solid tumors with documented KRAS, NRAS or BRAF mutations (NCT04892017).

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Cooperation between DCC-3116, a First-in-Class, Selective Inhibitor Of ULK1/2 Kinases, & KRAS^{G12C} Inhibition in Preclinical Models of NSCLC

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